

Reprinted from

Journal of
BIOLOGICAL REGULATORS
& Homeostatic Agents

**Transdermal transport by hydroelectrophoresis:
A novel method for delivering molecules**

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*Published in
J Biol Regul Homeost Agents 2001; 15: 381-2*



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Transdermal transport by hydroelectrophoresis: A novel method for delivering molecules

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Sir, Since the discovery of the needle and syringe researchers have been seeking less traumatic alternative methods for drug delivery, from iontophoresis to other more modern systems, such as cryoiontophoresis and transdermal systems (1). In view of the usefulness of these methods in medicine, a great deal of energy has been spent, especially in the last decade, to overcome the limitations of the scarce penetration of drugs during any novel procedure. Iontophoresis transports substances into tissues using an electrical current as a carrier. However, this method has limited efficiency in transdermal transport, resulting in the prevalently superficial distribution of the active substance. Cryoiontophoresis, a recently proposed improvement of this technique, uses a frozen solution of the active principle. However, among its various inconveniences, there is again a considerable superficial dispersion of the drug during treatment. To resolve these and other limitations, we have devised a novel method involving drug dispersion in an agarose gel vehicle and the use of electrophoretic mobility enhancers to provide the ideal ionic force for any principle to be transported. This method, denominated hydroelectrophoresis (2), uses a computerized instrument capable of producing electrical waves of variable form and frequency, programmed according to the depth which must be reached by the active principle. The system, consisting of a generator of current, 2 electrodes and biological tissue, is similar to a circuit in which the tissue represents the resistance to the passage of current. Resistance of the cell membrane is weak, whereas that of the skin is great. Hydroelectrophoresis is characterized by an iterative current consisting of a sequence of stimuli, separated by 1 second intervals, at a modulated frequency. This allows the molecules in a gel conductor to penetrate the skin barrier with a contemporary counterbalance by ions (for example, Cl^- and Na^+), as is observed in iontophoresis. However, at pH 4, the skin is a negatively-charged membrane and, due to the difference in the potential applied, a movement of non-dissociated molecules occurs through an electro-osmotic effect. This is highly advantageous because it permits transdermal passage of even neutral molecules. The electro-osmotic flux is generally given by the formula:

$$F = \frac{ZDI}{4hkn}$$

where Z represents the potential of the double strata, D the dielectric constant, I the current in Amperes, k the conductivity in ohms and n the viscosity coefficient. Because of the difference in potential, the electrophoretic effect moves the molecule more or less rapidly according to its electrophoretic mobility (EM) in relation to the formula:

$$EM = \frac{ZD}{4kn}$$

The pressure exerted by the applicator contributes to potentiate the transcutaneous transit through the streaming potential. All these physical processes influence the polarisation of the biological membranes, activating canals through which specific molecules penetrate. The instrument (Hydrofor®, Bioelectra, Reggio Calabria, Italy) consists of 2 main elements; the first is a source of electrical energy controlled by a microprocessor that regulates the variations and the second is a negative electrode (electrode dispenser) that polarizes the molecules in a gel solution contained in a vial. The other accessories consist of a positive electrode made of a 15.5 x 11 cm large silicon, rectangular, rubber plate, 2 snaps to fix the electrode dispenser and a provisionment wire. Disposable plates with connective wires are also available. The positive electrode is placed perpendicularly on the skin surface overlying the treatment area, with the interposition of gel and the therapeutic substance. The electrodes are connected to a computerized current supply. Varying the frequencies according to a precise wave equation ($Y = X - 180 + 2000$ where Y = frequency in Hz and X = depth in cm), it is possible to act on tissues at different depths, without interfering with the surrounding tissues.

To validate the hydroelectrophoretic method, we performed a study in an animal model, measuring the concentration of the active principles at the programmed depth with respect to the concentration in the gel solution applied on the skin surface. The cryoiontophoretic method was used as control.

Radiolabelled (^{125}I , 3800 cpm) progesterone solutions (Byk) were used for both hydroelectrophoresis and cryoiontophoresis. Radioactivity was measured with an automatic gamma-counter (SR 300 Tratec (Byk)). Eighteen New Zealand adult rabbits, mean weight 1.980 kg and shaven in the pubic and thoracic areas, were treated. Urine was withdrawn with a sy-

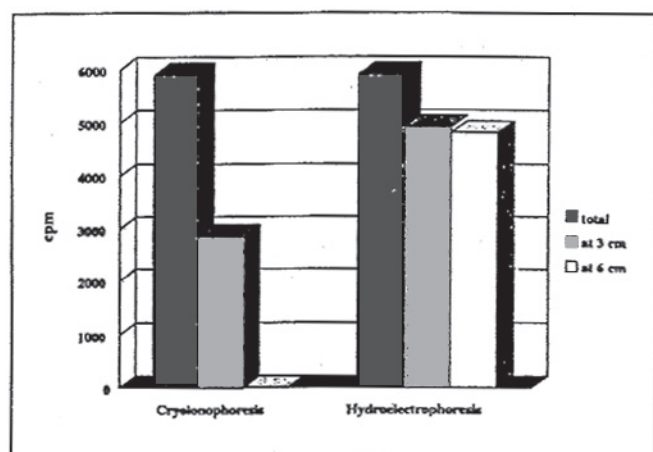


Fig. 1 - Comparison of cryoionophoresis and hydroelectrophoresis in transdermal transportation of ^{125}I labelled progesterone solutions. Columns indicate radioactivity measured as total before the experiments and at 3 and 6 cm.

ringe, guided by ultrasound. Blood samples were obtained by the auricular vein. All rabbits were treated with the radiolabelled progesterone: 3 groups, of 4 rabbits each, were treated with hydroelectrophoresis and the last group, divided into 3 subgroups of 2 rabbits, was treated by cryoionophoresis at a frequency of 500 Hz. During the hydroelectrophoretic procedure, the roller of the electrode dispenser was kept in constant rectilinear movement, applying mild pressure perpendicularly on the skin surface to favour the penetration of the gel product from the vial. Samples for determination of radioactivity were obtained in all rabbits at skin level, at 3 cm and at 6 cm depth. Tissues were homogenised and dissolved in 2.5 ml 1N NaOH and the radioactivity of the solution was measured. After hydroelectrophoresis, urine radioactivity was about 90% of the initial dose clearly indicating almost complete delivery of ^{125}I -labelled progesterone, while no trace was detected in blood samples after 30 minutes (data not shown). Figure 1 represents the comparison between cryoionophoresis and hydroelectrophoresis. After cryoionophoresis, a reduction of more than 50% of the ^{125}I content was observed, reaching close to zero when measured at 6 cm from the skin surface. On the other hand, when the same experiment was carried out by hydroelectrophoresis,

there was only a 20% reduction of radioactivity at 3 cm that was maintained at 6 cm depth.

Measurement of radioactivity indicates that cryoionophoresis is very inefficient in transdermal transportation. This result may be explained by the null electrophoretic mobility for solid substances, the minute radioactivity measured in tissues is due to fusion of the solid substance to the epidermis and the subsequent passage by ionophoresis. Hydroelectrophoresis, which utilises an agarose gel, improves migration of the radioactive compound under the effect of the electrical field and the solution creates an ideal ionic force that favours the transdermal passage of the radiolabelled progesterone.

We conclude that hydroelectrophoresis is an innovative and effective method for the transdermal transportation of both ionised and neutral drugs. Drugs may penetrate directly towards the area of the lesion without skin damage. Primarily clinical studies (3) indicate that hydroelectrophoresis is a new polyvalent and loco-regional therapeutic medical method for delivering drugs, applicable to almost all specialities.

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